STATISTICAL ANALYSIS PLAN (SAP)

This is a combined Statistical Analysis Plan (SAP) for the two studies named below:

Study Title:	A Phase I Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand veledimex in Subjects with Recurrent or Progressive Glioblastoma or Grade III Malignant Glioma	
Study Number:	ATI001-102	
Protocol Versions:	Amendment 3:	14March2016
	Amendment 2:	29January2016
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Study Title:	Protocol ATI001-102 Expansion Substudy 2.0: Evaluation of Ad-RTS-hIL-12 + veledimex in Subjects with Recurrent or Progressive Glioblastoma	
Study Number:	ATI001-102 EXP Substudy 2.0	
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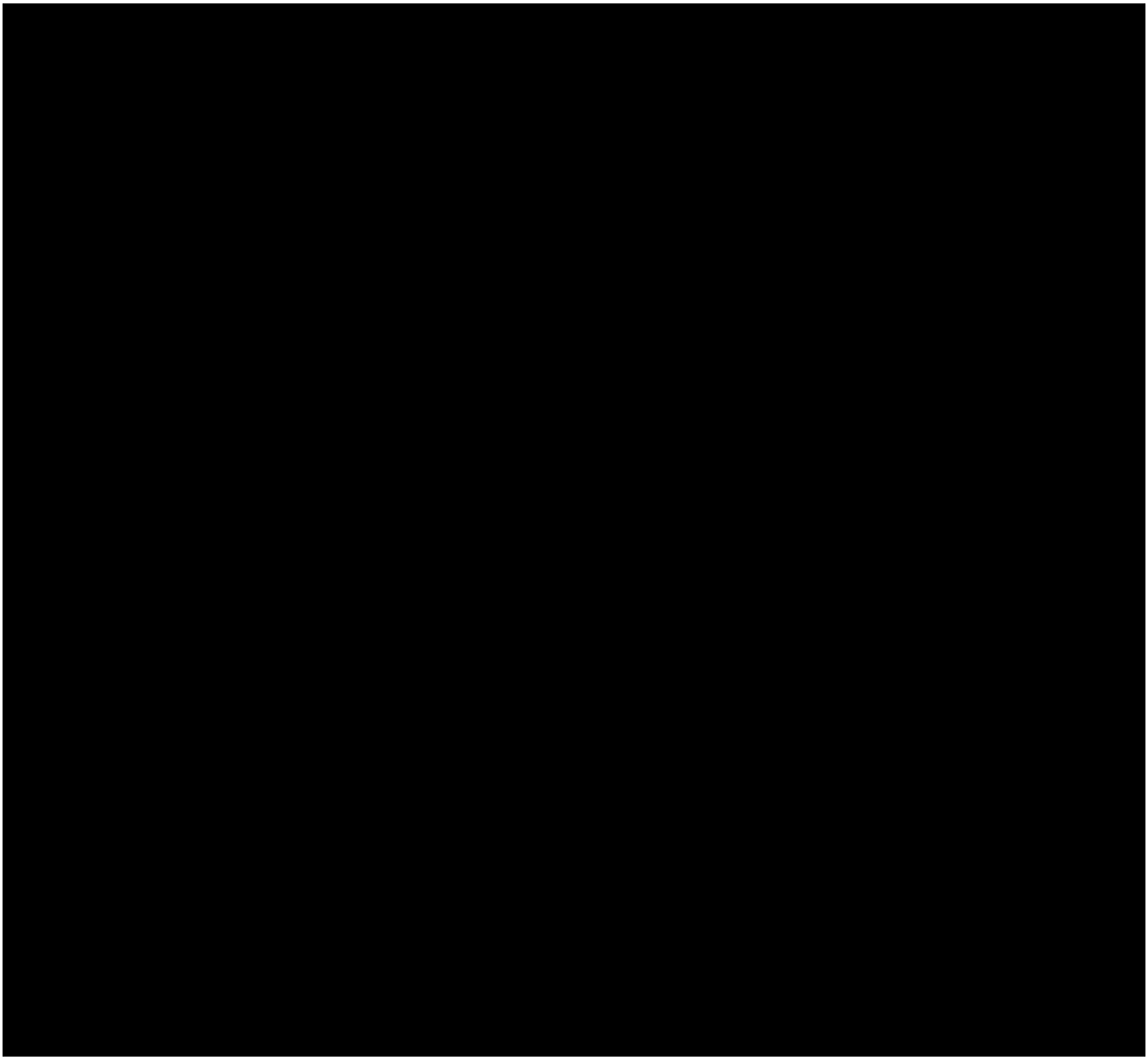
Sponsor:	Ziopharm Oncology, Inc.	
Version and Date:	Version 2.0, 13APR2021	

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

APPROVAL PAGE

This document has been prepared and/or reviewed by:



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LIST OF ABBREVIATIONS

Abbreviation	Term
mmol or mmol	Micromole
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-Time Curve
$AUC_{(0-¥)}$	AUC from Time Zero (pre-dose) Extrapolated to Infinite Time
$AUC_{(0-t)}$	AUC from Time Zero (pre-dose) to Time of Last observed Quantifiable Concentration Within a Subject Across all Treatments
BLQ	Below Limit of Quantification
BMI	Body Mass Index
b.i.d.	Twice Daily
BP	Blood Pressure
bpm	Beats per Minute
BUN	Blood Urea Nitrogen
C	Center
°C	Degrees Celsius
Ca	Calcium
Cl	Chloride
CLr	Renal Clearance
C_{max}	Maximum Observed Concentration
CMH	Cochran Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
Ct	Last Observed Quantifiable Concentration
DBF	Database Freeze
DBP	Diastolic Blood Pressure

DL	Deciliter
DOB	Date of Birth
dy	Days
ECG	Electrocardiogram
^{o}F	Degrees Fahrenheit
g	Grams
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transferase
HGB	Hemoglobin
ICD-9	International Classification of Diseases – 9th Edition
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
In	Inches
IP	Investigational Product
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
IU	International Units
K	Potassium
Kg	Kilogram
λ_z	Terminal Phase Rate Constant
L	Liter
Lb	Pounds
LDH	Lactate Dehydrogenase
LFTs	Liver Function Fests
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MAP	Mean Arterial Pressure
meq	Milliequivalent
mg	Milligrams
mL	Milliliter
mmHg	Millimeters of Mercury

Mo	Months
msec	Milliseconds
N	Total Sample Size
Na	Sodium
ng	Nanograms
NIMH	National Institute of Mental Health
OC	Observed Cases
OTC	Over the Counter Medication
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol Population
PT	Preferred term
RBC	Red Blood Cell Count
S	Sex
s.d.	Standard Deviation
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SR	Sustained Release
t	Time of Last Observed Quantifiable Concentration
$t_{1/2}$	Terminal Phase Half-Life
t_{max}	Time of Occurrence of Cmax
TG	Treatment Group
TIBC	Total Iron Binding Capacity
TS	Transdermal Delivery System-Placebo
UIBC	Unsaturated Iron-Binding Capacity
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell Count

WHO	World Health Organization
yr	Years

1. INTRODUCTION

Glioblastoma Multiforme (GBM) is the most common type of brain tumor and it is uniformly fatal. The community standard of treatment for this disease is gross or subtotal resection of the tumor, followed by radiation and temozolomide. Many challenges are encountered while trying to devise new drugs to treat GBM, such as the presence of the blood brain barrier which is impermeable to most drugs. Therefore, in the past few years attention was turned to immunological means for the treatment of this devastating disease. IL-12 mediates immuno-regulatory activities, including activating anti-tumor NK cells, memory T-cells, and cytotoxic T-cells, increasing local IFN-γ secretion, and reducing local immunoregulatory cells. These immuno-modulatory changes may result in tumor lysis, restoration of local immune function, and induction of immune response memory.

Systemic recombinant IL-12 in clinical trials has been effective in the treatment of cancer but has limited utility due to systemic toxicity. To circumvent these challenges and improve the therapeutic index, Ziopharm developed a gene therapy that permits well controlled local expression of IL-12 within the tumor microenvironment. Ziopharm is developing Ad-RTS-hIL-12 + veledimex for treatment of patients with GBM. The investigational product, Ad-RTS-hIL-12 + veledimex, is comprised of 2 components: Ad RTS-hIL-12 (Component 1) and veledimex (Component 2). Both components are necessary to produce the active moiety, human interleukin-12 (hIL-12).

This Statistical Analysis Plan will support the planned analyses for two clinical studies of Ad-RTS-hIL-12 + veledimex as monotherapy:

- Protocol ATI001-102 (will be herein referred to as ATI001-102 Main)
- Protocol ATI001-102 Expansion Substudy 2.0 (will be herein referred to as EXP Substudy)

Previously the SAP (Version 1.0, dated 05Apr2016) only described ATI001-102 Main.

The purpose of both studies was to evaluate the safety and tolerability of Ad-RTS-hIL-12 + veledimex as a monotherapy in subjects with recurrent or progressive. For additional details please refer to the current protocol, as indicated on the title page.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

ATI001-102 Main

- **Primary Objective**
  - To determine the safety and tolerability of varying doses of antitumoral Ad-RTS-hIL-12 plus oral veledimex doses in subjects with recurrent or progressive glioblastoma or Grade III malignant glioma.
- **Secondary Objectives**
  - To determine the MTD of veledimex when administered with varying doses of intratumoral Ad-RTS-hIL-12 dose
  - To determine the veledimex pharmacokinetic profile
  - To determine the veledimex concentration ratio between brain tumor and blood
  - To evaluate cellular [redacted] immune responses elicited by Ad-RTS-hIL-12 and veledimex
  - To determine investigator assessment of response including the tumor Objective Response Rate (ORR) and progression-free survival (PFS)
  - To determine overall survival (OS)

EXP Substudy

- **Primary Objective**
  - To determine the safety and tolerability of Ad-RTS-hIL-12 and veledimex (RTS activator ligand) in subjects with recurrent or progressive glioblastoma.
- **Secondary Objectives**
  - To determine the overall survival (OS) of Ad-RTS-hIL-12 + veledimex
  - To determine the veledimex pharmacokinetic (PK) profile
  - To determine the veledimex concentration ratio between the brain tumor and blood
  - To determine the Investigator's assessment of response, including tumor objective response rate (ORR), progression free survival (PFS), and rate of pseudo progression (PSP)

– To evaluate cellular [redacted] immune responses elicited by the combination treatment

2.2. Study Endpoints

The endpoints for both ATI001-102 Main and EXP Substudy were the same.

Primary Endpoint

The primary endpoint was the assessment of safety of Ad-RTS-hIL-12, administered by intratumoral injection plus veledimex, administered orally, as determined by the AE rate and the occurrence of DLTs analyzed specifically for each group.

Secondary Endpoints

The secondary endpoints are summarized as follows:

- Investigator Assessment of ORR and PFS
- Overall survival (OS)
- Veledimex concentration ratio between brain tumor and blood (Group 1, Day 0)
- Veledimex PK estimates starting at Day 1
- Correlative measures of immune response including serum cytokine levels [redacted]

3. PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD)

Please refer to the separate PK/PD SAP for a summary of the statistical analysis of PK/PD endpoints collected during monotherapy treatment of subjects.

4. STUDY DESIGN

Please refer to Appendix 1: Schedule of Study Procedures for the schedule of events for both ATI001-102 Main and EXP Substudy Other than the dose escalation component and the additional eligibility criteria, both ATI001-102 Main Group 1 and the EXP Substudy have the same schedule of events.

4.1. ATI001-102 Main

This is a Phase I study of Ad-RTS-hIL-12, administered as an intratumoral injection with escalating veledimex doses administered orally, in subjects with recurrent or progressive glioblastoma or Grade III malignant glioma. This study investigated the Ad-RTS-hIL-12 dose of

2 x 10^{11} vp and escalating veledimex doses to determine the veledimex maximum therapeutic dose based on the observed safety profile and in the presence of variable corticosteroid exposure.

This study was divided into three periods with an additional follow-up period:

- The Screening Period (Day -28 to -1):
  - After signing the informed consent, subjects entered the Screening Period to assess eligibility
- The Treatment Period (Day 0-14):
  - Eligible subjects were stratified into two groups according to clinical indication for tumor resection. Group 1 subjects underwent tumor resection and Group 2 subjects did not undergo tumor resection.
  - On Day 0, Group 1 subjects received one veledimex dose 3 ± 2 hours before the craniotomy resection procedure and Ad-RTS-hIL-12 administration. After the Ad-RTS-hIL-12 injection, veledimex was administered orally for 14 days, starting on Day 1 (for a total of up to 15 doses)
  - On Day 0, Group 2 subjects received Ad-RTS-hIL-12 by stereotactic injection and then subsequently took oral veledimex for 14 days, starting on Day 1 (for a total of 14 doses)
- The DLT evaluation period (Day 0-28), and
- The Follow-up Period (Day 28 [± 7 days], Day 56 [± 7 days] and every 8 weeks [± 7 days] thereafter).
- Survival Follow-Up (2 years from Day 0)

4.2. EXP Substudy

This is a multicenter Phase I study of an intratumoral injection of Ad-RTS-hIL-12 (2 x 10^{11}vp) and 20 mg of veledimex administered orally in subjects with recurrent or progressive glioblastoma.

This study was divided into three periods:

- The Screening Period (Day -28 to -1):
  - After signing the Informed Consent, subjects entered the Screening Period to assess eligibility.
- The Treatment Period (Day 0-14):

  - On Day 0, Group 1 subjects received one veledimex dose 3 ± 2 hours before the craniotomy resection procedure and Ad-RTS-hIL-12 administration. After the Ad-RTS-hIL-12 injection, veledimex was administered orally for 14 days, starting on Day 1 (for a total of up to 15 doses). The Follow-up Period (Day 28 [± 7 days], Day 56 [± 7 days] and every 8 weeks [± 7 days] thereafter).

- The Follow-up Period (Day 28 [± 7 days], Day 56 [± 7 days] and every 8 weeks [± 7 days] thereafter).

- Survival Follow-Up (2 years from Day 0)

5. INCLUSION AND EXCLUSION CRITERIA

5.1. Inclusion Criteria

As in the ATI001-102 Main protocol (changes for the EXP Substudy in bold)

1. Male or female subject ≥ 18 and ≤ 75 years of age

2. Provision of written informed consent for tumor resection, stereotactic surgery, tumor biopsy, samples collection, and treatment with investigational products prior to undergoing any study specific procedures

3. Histologically confirmed supratentorial glioblastoma or other World Health Organization (WHO) Grade III or IV malignant glioma from archival tissue **(EXP Substudy: Histologically confirmed supratentorial glioblastoma)**

4. Evidence of tumor recurrence/progression by MRI according to response assessment in neuro oncology (RANO) criteria after standard initial therapy

5. Previous standard of care antitumor treatment including surgery and/or biopsy and chemoradiation. At the time of registration, subjects must have recovered from the toxic effects of previous treatments as determined by the treating physician. The washout periods from prior therapies are intended as follows: (windows other than what is listed below should be allowed only after consultation with the Medical Monitor)
   a. Nitrosoureas: 6 weeks
   b. Other cytotoxic agents: 4 weeks
   c. Antiangiogenic agents, including bevacizumab: 4 weeks **[NOTE: short use (<4 doses) of bevacizumab for controlling edema is allowed]**
   d. Targeted agents, including small molecule tyrosine kinase inhibitors: 2 weeks
   e. Vaccine based therapy: 3 months
6. Able to undergo standard MRI scans with contrast agent before enrollment and after treatment

7. Karnofsky Performance Status ≥ 70

8. Adequate bone marrow reserves and liver and kidney function, as assessed by the following laboratory requirements:
    a. Hemoglobin ≥ 9 g/L
    b. Lymphocytes > 500/mm3
    c. Absolute neutrophil count ≥ 1500/mm3
    d. Platelets ≥ 100,000/mm3
    e. Serum creatinine ≤ 1.5 x upper limit of normal (ULN)
    f. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 x ULN. For subjects with documented liver metastases, ALT and AST ≤ 5 x ULN
    g. Total bilirubin < 1.5 x ULN
    h. International normalized ratio (INR) and activated partial thromboplastin time within normal institutional limits
9. Male and female subjects must agree to use a highly reliable method of birth control (expected failure rate less than 5% per year) from the Screening Visit through 28 days after the last dose of study drug. Women of childbearing potential (perimenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential) must have a negative pregnancy test at screening.

5.2. Exclusion Criteria

As in the ATI001-102 Main protocol (changes for the EXP Substudy in bold)

1. Radiotherapy treatment within 4 weeks or less prior to starting first veledimex dose

2. Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures

3. Known immunosuppressive disease, autoimmune conditions, and/or chronic viral infections [e.g., human immunodeficiency virus (HIV), hepatitis]

4. Use of systemic antibacterial, antifungal, or antiviral medications for the treatment of acute clinically significant infection within 2 weeks of first veledimex dose. Concomitant therapy for chronic infections is not allowed. Subjects must be afebrile prior to Ad-RTS-hIL-12 injection; only prophylactic antibiotic use is allowed perioperatively.

5. Use of enzyme inducing antiepileptic drugs (EIAED) within 7 days prior to the first dose of study drug. Note: Levetiracetam (Keppra®) is not an EIAED and is allowed

6. Other concurrent clinically active malignant disease, requiring treatment, with the exception of non-melanoma cancers of the skin or carcinoma in situ of the cervix or nonmetastatic prostate cancer.

7. Nursing or pregnant females

8. Prior exposure to veledimex

9. Use of medications that induce, inhibit, or are substrates of CYP450 3A4 within 7 days prior to veledimex dosing without consultation with the Medical Monitor

10. Presence of any contraindication for a neurosurgical procedure.

11. Unstable or clinically significant concurrent medical condition that would, in the opinion of the investigator or medical monitor, jeopardize the safety of a subject and/or their compliance with the protocol. Examples include, but are not limited to, unstable angina, congestive heart failure, myocardial infarction within 2 months of screening, ongoing maintenance therapy for life threatening ventricular arrhythmia or uncontrolled asthma.

Exclusion Criteria specific to the EXP Substudy:

12. Previous treatment with bevacizumab for their disease [NOTE: short use (< 4 doses) of bevacizumab for controlling edema is allowed)

13. Subjects receiving systemic corticosteroids during the previous 4 weeks.

6. DOSE ESCALATION DECISION RULES FOR ATI001-102 MAIN

Dose escalation decision rules were based on a standard 3+3 design modified to independently evaluate the two stratified subject groups that may exhibit different safety and tolerability profiles. The dose escalation rules were applied to subjects who received Ad-RTS-hIL-12 and at least one veledimex dose post Ad-RTS- hIL-12 administration. A formal Safety Review Committee (SRC) and Data Safety Monitoring Board (DSMB) along with an SRC/DSMB charter was written to facilitate dose escalation decisions.

- Members of the SRC were comprised of the study Investigators, the Medical Monitor, and other appropriate Ziopharm representatives.

- The DSMB was an independent multidisciplinary group consisting of clinicians with experience in management of patients with GBM and in the conduct and monitoring of clinical trials.

In the standard 3+3 design, the MTD is defined as the dose level below at which more than 33% of subjects of the same cohort and group experience DLTs. If two DLTs occurred in the same cohort in a group (two DLTs in Group 1 or two DLTs in Group 2) dose escalation halts in the group experiencing the DLTs. The MTD will then be explored in six subjects of the same group at the next lower dose level and will be declared to be the dose in which less than 33% of subjects experience DLTs. Intra-subject dose escalation is not permitted. An intermediate dose cohort may be explored during the dose escalation phase, as deemed necessary and/or as recommended by the SRC.

Dose escalation proceeded along the lines of the following.

- In each cohort, the first subject was monitored for the 14 days of treatment and then observed for an additional seven days post the last veledimex dose before the second and third subjects were enrolled in that same cohort.

- At the end of each cohort, the SRC convened to review the safety data after the third patient in a cohort, within a group, completed veledimex dosing and had been monitored for 28 days after the Ad-RTS-hIL-12 injection.

- Originally, each dose cohort was to enroll three subjects from Group 1 and three subjects from Group 2. If no DLTs occurred among the first three subjects in a cohort, within the same group, dosing to the next higher dose cohort could proceed after the SRC and DSMB provided a recommendation to proceed.

- In any cohort, if one DLT occurred among the first three subjects within the same group, three additional subjects of the same group were to be enrolled.

- If one or more of the three additional subjects experienced a DLT (e.g. two DLTs in Group 1 or two DLTs in Group 2), then dose escalation was halted.

  – The SRC would convene to evaluate safety, determine if the MTD had been reached and decided whether to stop treatment or de-escalate veledimex dosing in that group.

- In the event that the SRC determined that a DLT would not be considered to be contributory to the MTD, a decision was made about enrolling additional subjects prior to determining the MTD.

Originally, the study was planned to explore four veledimex dose cohorts of 20 mg, 40 mg, 80 mg and 120 mg once daily, and two doses of Ad-RTS-hIL-12 ($2x10^{11}$vp and $1x10^{12}$vp). The actual dose cohorts were treated at 10mg, 20mg, 30mg and 40 mg of veledimex. Only one dose of Ad-RTS-hIL-12 was explored ($2x10^{11}$vp).

Originally, expansion cohorts were not prospectively planned in this study. If ≥ 33% of subjects in the expansion cohort experience DLTs, according to the definition used in the dose-escalation phase, additional subjects might have been enrolled at the next lower dose tested in the dose escalation phase, or at an intermediate dose, as recommended by the SRC. Intermediate cohorts and an expansion cohort were explored in Group 1 as noted below.

Group 1 – Following the completion of Cohort 1, the SRC and DSMB approved dose escalation to Cohort 2, as per protocol. Three of six subjects in Cohort 2 experienced a DLT and therefore this dose was deemed the maximum administered dose (MAD). The SRC and DSMB approved opening an intermediate cohort of 30mg to determine the MTD. At the conclusion of this cohort the SRC determined due to veledimex compliance rates, that an expansion cohort of 20mg should be explored. Following this cohort, further the SRC approved an intermediate cohort of

10mg. At the conclusion, based on veledimex compliance and OS rates, 20mg was determined to be the optimal dose.

Group 2 – Following the completion of Cohort 1, there was a Ziopharm decision to not move forward with dose escalation. This was not a safety related decision.

7. SAMPLE SIZE

7.1. ATI001-102 Main

The choice of the number of subjects was based on the standard 3+3 design modified to independently evaluate two stratified subject groups that may exhibit different safety and tolerability profiles.

- In general, up to 72 subjects could have been enrolled into this study, including three to six subjects per group enrolled in each of the planned dose level cohorts. Subjects who withdraw from the study during the dose-limiting toxicity (DLT) evaluation period (Days 0-28) for reasons other than toxicity or disease progression could have been considered to be replaced.

- The sample sizes chosen were based on clinical consideration for a standard 3 + 3 dose escalation design to determine the MTD for two separate groups of subjects independently evaluable for safety and dose escalation. Power calculations for comparison of AE rates are simply too inexact to be clinically meaningful because the AE rates are unknown and cannot even be approximately projected.

- If an AE occurs at a rate of 1% or 10%, then the chance for observing such an AE among six subjects receiving that dose will be 6% and 47% respectively. If no AE is observed in any of the six subjects, then the true incidence is at most 24% with 80% confidence and 32% with 90% confidence.

7.2. EXP Substudy

Sample size statistical considerations were provided as similar to those of ATI001-102 Main.

- A total of 36 treated subjects in the EXP Substudy provided for a total sample size of 52 treated subjects with combination Ad+V (FAS) at Ad-RTS-hIL-12 (2 x10^{11} vp) and 20mg of veledimex

- A total of 51 treated subjects received both Ad-RTS-hIL-12 (2 x10^{11} vp) and 20mg veledimex.

- If no AE events occur in approximately 50 subjects, then an AE rate as low as 6% could be ruled out with 95% confidence.

8. ANALYSIS POPULATIONS

Screen Failures

- Screen Failures are subjects who signed an informed consent and either did not meet the eligibility criteria per protocol or subsequently withdrew consent before receiving any study treatment. The number of subjects classified as screen failures will be summarized in the subject disposition.

FAS Population

- The Full Analysis Set (FAS): Overall Safety Population (OSP) includes all subjects who have received at least one dose of veledimex (pretumor resection and) and/or all subjects who received Ad-RTS-hIL-12.

ESP Population

- The Evaluable Safety Population (ESP) includes subjects who have received Ad-RTS-hIL-12 and at least one dose of veledimex after Ad-RTS-hIL-12 administration.

ITT Population

- In general, the ITT population is defined for randomized controlled trials. In this uncontrolled setting, the FAS plays the same role as the ITT.

Per-Protocol (PP) Population

- The ESP is denoted as the PP population in this uncontrolled setting.

PK Population

- All Subjects with available serum-time concentration data are included in the PK Population.

Completers

- The completers population is defined as all eligible subjects who survived two years from Day 0 without any major protocol deviations. In this uncontrolled setting of the rGBM almost all subjects died before two-years of follow-up. This population is not described for the purpose of statistical analysis.

9. GENERAL ANALYSIS CONSIDERATIONS

9.1. Data Presentation

Originally, when the SAP for ATI001-102 Main was finalized, there was no plan to combine ATI001-102 Main with the EXP Substudy. However, after further consideration, for practical purposes, combining the SAP and analysis helps facilitate performing the long-term OS analysis as well as identify any potential patient characteristics which could be important for late-stage clinical trial planning. All final analyses will summarize comparisons of subjects treated with 20 mg veledimex in ATI001-102 Main (n=15 ESP subjects) combined with the subjects treated with 20 mg veledimex in the EXP Study (n=36 ESP subjects).

The summary tables will be presented as follows:

- **The Parent Table Header** (N=75 FAS subjects enrolled in ATI001-102 Main and ATI001-102 Expansion)
  - Group 1 Craniotomy: 68 subjects over 5 veledimex dosing cohorts combining all treated subjects from ATI001-102 Main and the EXP Substudy
  - Group 2 Stereotactic: 7 subjects treated at 20mg veledimex
- **Table A Header** (N=39 FAS subjects Enrolled in ATI001-102 Main)
  - Group 1 Craniotomy: 32 subjects over 4 veledimex dosing cohorts from ATI001-102 Main
  - Group 2 Stereotactic: 7 subjects treated at 20mg veledimex in ATI001-102 Main
- **Table B Header** (N=52 FAS subjects dosed at 20mg veledimex enrolled in ATI001-102 Main and ATI001-102 Expansion)
  - ATI001-102 Main, Group 1 (craniotomy): 16 subjects
  - ATI001-102 Expansion: 36 subjects

Table 1: Example Summary Table Shell

Parent Table Header (N=75)							
Group 1: Intracranial						Group 2: Stereotactic	All Combined
	Main Study Veledimex Dose				Expansion Veledimex Dose	Main	
	10mg/ day	20mg/ day	30mg/ day	40mg/ day	20mg/day	20mg/day	Combined
	n =6	n=16	n =4	n =6	n =36	n =7	N =75
Table A Header (Main Study N=39)							
Group 1: Intracranial						Group 2: Stereotactic	
	veledimex Dose					Main	
	10mg/ day	20mg/ day	30mg/ day	40mg/ day		20mg/day	Combined
	n =6	n=16	n =4	n =6		n=7	N =39
Table B Header (N=52)							
Group :1 Intracranial (treated at 20 mg veledimex: Main: n=16; EXP: n=36; Combined N=16+36=52							
	Main veledimex Dose				Expansion		
		20mg/ day			20mg/day		Combined
		n=16			n =36		N=52

The listing conventions for combining the data for all treated FAS subjects (n=75) are organized as follows:

- All listings will be ordered by ATI001-102 Main to be followed by the EXP Substudy
  - ATI001-102 Main Group 1, veledimex dose (10mg, 20mg, 30mg, 40mg) and subject number
  - ATI001-102 Main Group 2, veledimex dose (20mg) and subject number
  - EXP Substudy, veledimex dose (20mg) and subject number
- Listings will present all available data.

9.2. Populations Used in the Presentation of Statistical Summaries

The following subject populations will be evaluated and used for presentation and analysis of the data:

- The FAS will be used for summaries of baseline characteristics and safety. Summaries will be presented by group and veledimex dose.
- The ESP is to be used for analysis of dose limiting toxicities, overall survival and progression free survival and finding the maximum tolerated dose. The ESP will also used for the PD/biomarker data analysis.
- The Pharmacokinetic Population (PKP) includes all subjects who received veledimex and have PK samples to be measured (please refer to the PK/PD SAP for details)
- Summaries of dose limiting toxicities are described for ATI001-102 Main Group 1 and not Group 2
  - Group 2 subjects were only treated at 20mg veledimex and no DLTs were observed.
  - DLTs only apply to ATI001-102 Main

9.3. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Major protocol deviations are a divergence from the protocol that could materially: (a) impact the integrity or analyzability of the resultant data, (b) contradict the Informed Consent Form (ICF), (c) impact a subject's safety, rights, or welfare. In general, no subject was planned to be removed from any analysis population because of a protocol deviation.

A planned protocol deviation (i.e., waiver), is a deviation from the protocol that has been submitted, reviewed, approved, and documented prior to the deviation occurring.

Deviations will be identified as either Major, Minor, or Exemption (waiver). Deviations will be identified as such and listed by patient and study center. Major deviations that are considered to potentially impact the efficacy or safety analyses will be tabulated. Protocol deviations will be listed and summarized by type.

- Deviation from inclusion/exclusion criteria (may also be listed under waiver)
- Withdrawal criteria met during the study, but subject was not withdrawn.
- Prohibited concomitant medications
- Treatment deviation
- Other protocol deviation

9.4. Multicenter Studies

Both the ATI001-102 Main Study and Expansion substudy have enrolled subjects from multiple investigative sites. There is no plan to present the data by investigative site. Subject listings will indicate the investigative site as part of the subject ID (first three digits, i.e., 457-XXX is Site 457).

9.5. Other Strata and Covariates

Exploratory analysis of subject characteristics has been previously described where applicable.

9.6. Examination of Subgroups

Previously described in Exploratory Analysis of OS. See Section 12.1 for more analyses.

9.7. Multiple Comparisons and Multiplicity

No formal comparisons.

9.8. Interim Analysis

There were no formal preplanned interim analyses.

10. DATA HANDLING CONVENTIONS

The data conventions for all treated FAS subjects (n=75) are as follows:

10.1. Missing Data

- In general, no imputations for missing or partial data will be made.
- In analyses presented over time by visit, no imputations will be performed on missing data. All analyses will be based on the observed data. The effective sample sizes at each assessment visit will be based on the total number of subjects with non-missing data for the parameter of interest at that visit.
- Unless otherwise specified, percentages will be calculated based on the number of subjects based on non-missing data as the denominator.
- A missing values category will also be defined to ensure all subjects are accounted for in prespecified populations for analyses.
- In general, other than for partial dates, missing data will not be imputed and will be treated as missing.

- The algorithms for imputation of partial dates vary depending on the parameter. These will be provided in the programming specifications that will be prepared for this study.

- When applicable, unless otherwise specified, the following general imputation rules will be used for missing date in the assessment of an event:

  - If all parts of the date are missing, the date will not be imputed.

  - In the case where only the start day of an event is missing, it will be replaced by the start day of study treatment if the event occurs in the same month and year. Otherwise, it will be replaced by the first of the month.

  - If the stop day is missing, the stop day of the event will be replaced by the stop day of study treatment. Otherwise, the last day of the month will be used to replace the missing stop day.

  - If both the start day and month of an event are missing, the start day and month will be replaced by the start day and month of study treatment if the event and the start of the treatment occur in the same year; otherwise, it will be replaced by 1st of January.

  - All imputed dates must be prior to the dates of withdrawal of consent, lost to follow-up, and death.

10.2. Baseline Data

- Unless otherwise specified, baseline is the last observation before the first study drug administration. The baseline lesion assessment is considered to be the one within 72 hours following Ad-RTS-hIL-12 administration.

- If the schedule of events includes a baseline value (i.e., Day 0 lab just before study drug administration) that is not collected as planned for any reason, then the data collected for the variable known to be the last observation before the first dose of study drug will serve as the baseline value (i.e., Screening value).

- In addition, the relevant section for each endpoint will describe the baseline values of subjects recorded as taken before study treatment according to schedule along with subjects for whom measurements should have been taken before study treatment but for whom those measurements were taken after study dosing was received.

- Change from baseline is performed for Serum Chemistry, Hematology, Urinalysis, Vital Signs, ECG Results and the Karnofsky Performance Status (KPS) Score.

10.3. Measurements Collected from Subjects Excluded from Predefined Analysis

- Populations or extra measurements that were repeated or obtained based on unscheduled visits may not be included in summary tables unless specified.
- Regardless of data inclusion for any analysis
  - Subject Listings will present all available data received in the electronic CRF (eCRF)
  - Where applicable subject listings will also present all final data received from data sources for which data external to the eCRF were captured for which data transfer agreement specifications were established.

10.4. Derived and Computed Variables

- Day 0 corresponds to the date of Ad-RTS-hIL-12 administration.
  - Then more generally, Day n represents the elapsed number of days from Day 0, inclusive.
  - Day n = Date of assessment – Date of Day 0
  - Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to Day 0. Day −1 will be the day before Day 0, and in general, negative days will be measured backwards starting from Day −1.
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded up to 1 significant digit for purposes of presentation.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded up to 1 significant digit for purposes of presentation.
- Age will be calculated in years relative to the date of informed consent based on the following SAS statement: Age = floor ((intck('month', date of birth, date of informed consent) – (day (informed consent) < day (date of birth))) / 12 (Check with LLX and Ziopharm Programming)
- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- Pregnancy test data will be listed only.

10.5. Reference Section 11.1 for derived study variables were created based on clinical interpretation of the eCRF data for the 20mg cohorts in ATI001-102 Main and the EXP Substudy. Continuous Variables

- Summary statistics will be provided for continuous variables (e.g., age).
- Unless otherwise stated, this will consist of the number of subjects with a non-missing value of the variable (n), mean, standard deviation, median, minimum, and maximum.
- The same number of decimal places as in the raw data will be presented when reporting minimum and maximum.
- One more decimal place than in the raw data will be presented when reporting mean and median.
- Two more decimal places than in the raw data will be presented when reporting standard deviation.

10.6. Categorical Variables

- Frequency counts will be provided for categorical variables (e.g., gender)
- Unless otherwise stated, this will consist of the number of subjects with a response in a particular category and the percentage of the total number of subjects in that column. Unless otherwise stated, missing responses will be included in both the display and in the calculation of percentages (i.e., they will be included in the denominator).
- Percentages will be rounded to one decimal place.
- Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

10.7. Visit Windows

The statistical analysis planned for this study will be performed according to the actual visit dates and times and do not require the calculation of visit windows. However, for analyses that require a particular visit as planned, measurements included in that visit must have occurred during the acceptable window defined for the visit in the protocol, unless otherwise specified in this plan. As needed, visit windows will also be created for analysis, to include data collected at unscheduled visits. Visit windows will apply to all treatment arms. When multiple visits occur within the same window, the visit closest to the target visit day will be selected. When two visits are equidistant from the target day, the visit occurring latest in the window will be used for analysis.

11. CONVENTIONS

- SAS version 9.4 or higher will be utilized for all data analyses, summary tables, subject listingsand figures. Derived datasets are also created using (SAS®) software.
- The definition of all derived variables and decodes for coded data must appear in the notes.
  - Due to space limitations, tables and listings may require a page of notes as a one-time preface to the output.
- In general, summary tables and listings (e.g., post text tables and individual subject data listings) include a "footer" providing explanatory notes that indicate at a minimum:
  - Date of data extraction
  - Date of output generation
  - SAS complete program name, and path where it is stored.
  - including the path that generates the output.
  - Any other output specific details that require further elaboration (e.g. CRF pages from which the data were obtained)

Post text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is locked to ensure the replication of the results.

In general, the listings should be sorted and presented by treatment assignment, investigational site, and subject number. Treatment assignment and site can appear in the banner of the listing.

- From left to right, the subject number, visit number, visit date, and relative day should appear.
- WHO -DD March 2016:
- MedDRA Version 23.0 or higher Data Management
- The database consists of data collected for (Ad+V) monotherapy treated subjects in ATI001-102 Main (n=39) and in the EXP Substudy (n=36) for a total of N=75 full analysis set (FAS) subjects.
  - In addition, data collection outside of the eCRF as part of the totality of the data to be finalized is derived from 7 external data sources denoted as "vendors" (Table 2)

- Of the [redacted] listed, data from 6 of the 7 need to be finalized for ATI001-102 Main and the EXP Substudy
- The imaging data objective originally to be undertaken with [redacted] was put on hold. Subsequently it was decided that it would not be continued for the EXP Substudy.

- For completeness it is noted that there are subjects who also have data in the database who are classified as screen failures for whom we are not counting for the purpose of this description. Subjects that were enrolled but did not receive treatment were withdrawn and not included in any analysis population.
- Currently the data for EXP Substudy (n=36) are being reviewed for finalization in order to declare the Monotherapy database finalized and ready for statistical analysis based on this revised SAP.
  - The ATI001-102 Main EDC database has already been locked. Following the completion of lab reconciliation, database lock signoff will be complete per SOP.
  - The Raw SAS datasets have been previously converted into SDTM SAS datasets and converted to ADaM for producing TLF'S according to specifications previously provided by Ziopharm Biostatistics to a third party Statistical CRO.
- Preparation for locking the EXP Substudy database will occur when all subjects (n=36) have been reviewed and it has been established that there are no outstanding queries to be resolved.

Table 2: Vendors for Data Collection Outside of eCRF

Vendor	Analysis	ATI001-102 Main	EXP Substudy
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]

Table 2: Vendors for Data Collection Outside of eCRF (Continued)

Vendor	Analysis	ATI001-102 Main	EXP Substudy
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

11.1. Derived Data from Overview Book

Derived data variables found in the ADaM were constructed based on SAS programming specifications using data captured on the eCRF. In some instances, un-preplanned derived study variables were created based on clinical interpretation of the eCRF data for the 20mg cohorts in ATI001-102 Main and EXP. These variables were captured in a clinical "Overview Book" (OB).

The OB variables are:

- Current IDH Status, Current MGMT Status – source: EDC and Neogenomics Laboratories
- Number of Prior Lines of Treatment – source: EDC
- Recurrence Status – source: EDC

Additionally, the definition of Cytokine Release Syndrome per the Investigator's Brochure, was applied to all subjects in both studies:

- CRS classification based on EDC entry of adverse events, laboratory assessments, and vital signs for which the judgment of severity grading was deduced.

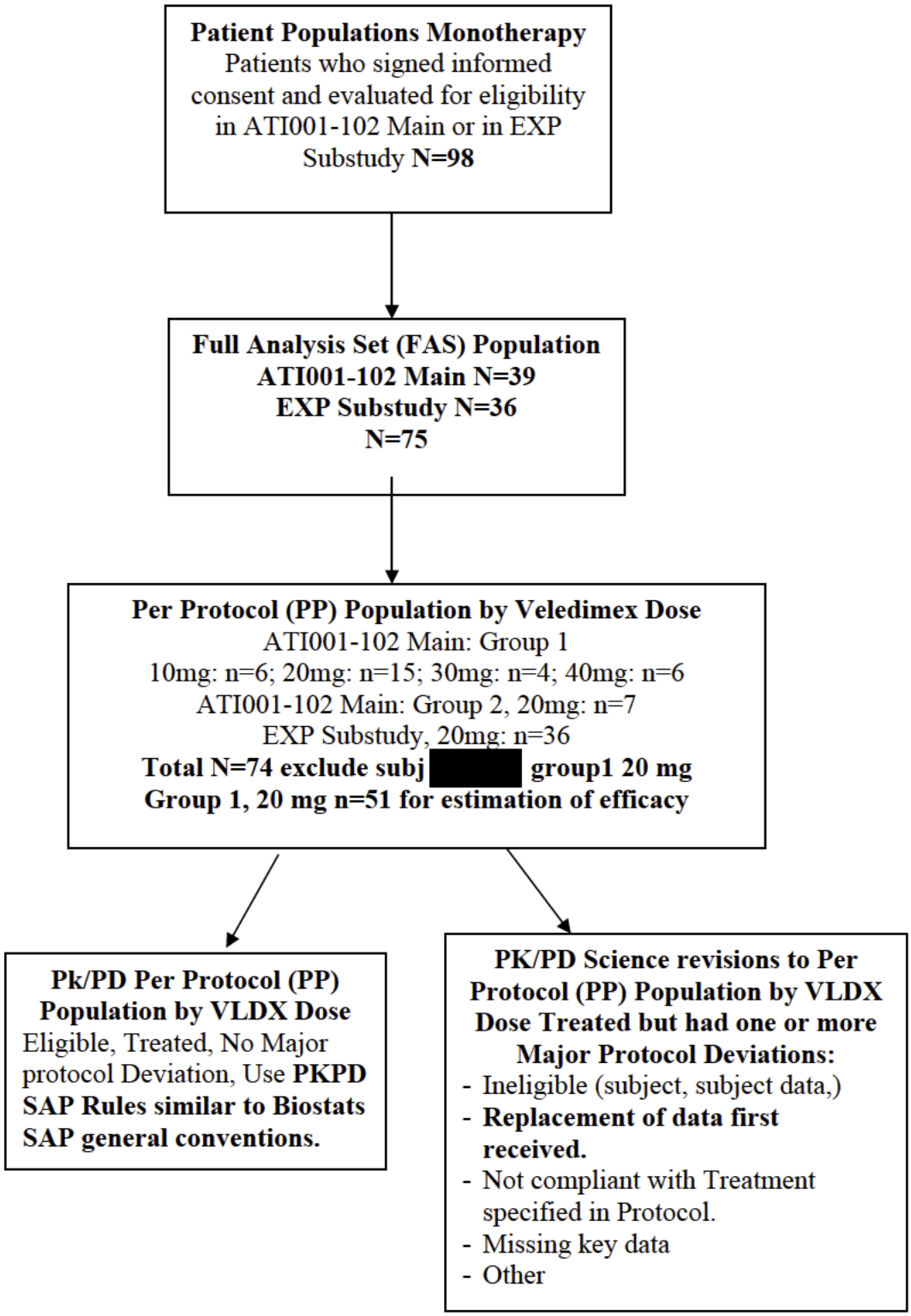
The Overview Book variables used for the purpose of the TLFs and the CRS assessment will be internally reviewed and approved by Ziopharm clinical development personnel and this documentation will be filed in the TMF. These two documents will clearly differentiate those derived variables obtained from the SDTM from those variables derived by Ziopharm Study Subjects.

11.2. Subject Disposition

Subject disposition summaries will include the number of subjects enrolled and treated in each dosing cohort for the FAS population. Figure 1, illustrates,

- The number of subjects screened N=98
- N= 75 subjects are classified as belonging to the FAS.
- N =74 PP subjects also denoted as the ESP
- In order to provide for flexibility of analyses, there are two sub sections denoting:
    - Biostatistics statistical considerations for which data handling rules and populations for analyses are determined for PK/PD variables
    - PK/PD Scientist determination of statistical considerations for which data handling rules and populations for analyses are determined for PK/PD variables
        - Refer to the PK/PD statistical analysis plan where applicable for potential deviations from this SAP.
        - Such departures could be well suited to scientific data influences that may not be captured from a Biostatistics perspective.

Figure 1: Patient Populations



- The number and percent of subjects who discontinue from the study will be summarized by reason for discontinuation by dosing cohort, group and overall.
- The number and percentage of subjects in each analysis population will be tabulated.
  - If applicable, major protocol deviations will be summarized and listed.
- Subjects who are screen failures will be summarized in the combined column
  - ATI001-102 Main study screen failures under Table A Header
  - EXP Substudy screen failures under Table B Header
  - Combined screen failures for both ATI001-102 Main and the EXP Substudy summarized under the Parent Header Combined column

12. SUBJECT CHARACTERISTICS AND SUBGROUPS

Demographics

Demographic and baseline variables including age, sex, ethnicity and race, will be summarized by dose cohort treatment arm in ATI001-102 Main, the EXP Substudy and all subjects combined for the FAS. Age will be calculated relative to date of informed consent and will be summarized using descriptive statistics as well as by the number and percent of subjects in age categories (< 65, ≥ 65 years). Similarly, height and weight will be summarized using descriptive statistics. Sex, ethnicity and race, will be summarized with the number and percent of subjects in each parameter category.

Age is taken to be the subject's age on the date of the Screening visit. Conversions for height and weight are as follows:

- Height (cm) = Height (inches) x 2.54
- Weight (kg) = Weight (lb) x 0.454

Demographics will be listed and tabulated using descriptive statistics.

Medical History

Medical history will be summarized for among other things:

- Prior cancer treatment,
- Initial diagnosis of high-grade glioma

  - along with the time in months since initial diagnosis,
  - grading and type at time of initial diagnosis, and at screening will be tabulated.
- Current disease status.
- Medical/surgical history will be captured and listed.

Prior cancer treatment information will be tabulated.

- This will include whether the subject had any previous treatment, treatment type and the best responses from any previous treatments.
- Other aspects of the patients' medical history that are unrelated to their underlying malignancy, along with any abnormal findings noted during the screening physical examination will be presented in data listings.

12.1. Subject Characteristics Subgroups

Baseline subject characteristics will be summarized for the FAS by dose cohort treatment group in ATI001-102 Main, the EXP Substudy and all subjects combined.

Among the patient factors to be explored for comparability are the following patient characteristic subgroup derived variables:

- Age category: <65 vs. ≥65
- Gender: female vs. male
- MGMT: unmethylated vs. methylated
- Hispanic or Latino: yes =1 vs. no=0
- Race: white vs. not White
- IDH: wild type vs. mutated
- Prior Steroid: yes=1 vs. no=0
- Enhanced Lesion: unifocal vs. multifocal
- Prior Number of Lines of Treatment: 1 vs. GT 1
- Steroid Cumulative Dose Up to 14 days: ≤ 20mg vs. >20mg
- Number of Lesions at Entry: 1 vs. > 1
- KPS Screening, N(%): ≥70 to 90 vs. ≥90

- Veledimex Dosing Compliance: ≥80% vs. <80%
- Number of Recurrences: 1st recurrence vs. ≥ 2 recurrences

12.1.1. Subgroup Analysis for Subjects Receiving Anti-Cancer Therapies Post Ad+V

Exploratory analysis will define a subgroup of Subjects documented as receiving any Anti-Cancer Therapies post Ad+V:

- Subjects documented as having received any anti-cancer therapies post treatment of controlled Ad+V will be summarized to supplement the analysis of BOR as a potential surrogate endpoint for OS.
- Determine Proportion of subjects documented as receiving any Anti-Cancer Therapies post Ad+V.
- Estimate OS for this subgroup.
- Provide listing of this subgroup to include identification of anti-cancer treatment.

12.2. Previous and Concomitant Medications

All prior and concomitant medications consumed through Day 56 will be recorded and coded using the anatomic-therapeutic-class (ATC) coding system. MedHX and WHO-DD V (March 2016) is used to code CMEDS. Details of concomitant medication will be listed.

- Medications will be tabulated according to whether they were being taken pre-study and/or during the study.
- Medications received in the period preceding consent (28 days) in addition to those ongoing at screening will be captured in the CRF.
- Concomitant medications are those medications being taken on or after the first dose of study medication.
  - If the start and stop dates of the medications do not clearly define the period(s) during which a medication was taken, it will be assumed to have been a concomitant medication.
- Previous and concomitant medications will be tabulated by preferred term and ATC term 2.
- Non-pharmacological concomitant measures (e.g., procedures) will be listed.

13. SAFETY ANALYSIS

Clinically significant changes in the subject's physical examinations, vital signs, ECG evaluations and abnormal laboratory test results, will be captured as AEs. Safety evaluations will use calculations to determine estimates of the incidence, intensity, and the type of AE and SAE's based on preferred term coding. AEs, ECG findings, and vital signs will be tabulated and presented for all subjects in the study, presented by dose cohort and group.

All clinical findings will be further inspected through a clinical review of relevant parameters including AEs, serious adverse events (SAEs), laboratory values (hematology, serum chemistry, and urinalysis), body weight, vital signs, physical examinations, and ECOG performance status. Safety analysis will be carried out for the FAS Safety Population in general. Where applicable the Safety will also be summarized using the ESP.

Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

13.1. Maximum Tolerated Dose/ Dose Limiting Toxicities Study Drug Exposure for ATI001-102 Main

The protocol defines the MTD as the dose level below at which less than 33% of subjects, of the same cohort in a group, experience DLTs, with an independent assessment of Group 1 and Group 2 subjects. The EXP Substudy was one fixed dose and therefore MTD does not apply.

- The number of DLTs and the proportion of subjects with any DLT and each type of DLT will be summarized by veledimex dose within each group.
- The ESP will be used for summaries of DLTs.
  - DLT data will also be listed by veledimex dose and subject within each group.

Dose-limiting toxicity (DLT) is defined as:

- An event, occurring within the first 28 days (Day 0 - Day 28) that meets one of the following conditions:
  - Any local reaction that requires operative intervention and felt to be attributable to Ad-RTS-hIL-12 and/or veledimex.
  - Any local reaction that has life-threatening consequences requiring urgent intervention or results in death and felt to be attributable to AdRTShIL12 and/or veledimex.
  - Any Grade 3 or greater non-hematological adverse event that is at least possibly related to the study drug.
  - Any Grade 4 hematologic toxicity that is at least possibly related to the study drug and lasts at least 5 days.

- Grade 3 or higher thrombocytopenia at least possibly related to the study drug

Note: diagnostic brain tumor biopsy is not considered a DLT. Seizures, headache, and cerebral edema are commonly observed in this population and will be recorded according to grade of toxicity but will not be considered a DLT unless they are deemed as most likely to be drug-related as the main contributory factor.

Details of study drug administration and dose modifications will be listed as follows:

- Ad-RTS-hIL-12
  - Total volume received, number of sites and whether the dose was modified will be tabulated.
- Veledimex
  - The total dose received (mg) for each study treatment will be calculated based on the Drug Accountability CRFs including the oral dosing diaries. Dosing details are summarized per subjects for each dosing cohort. Dose and dose modifications per subject treated will be listed. The number of doses received will be tabulated.
  - Subject veledimex dosing compliance will be determined for each subject as the total number of tablets dispensed minus the total number of tablets reported as not taken, divided by the total number of tablets dispensed, multiplied by 100.
  - Subgroups for dosing compliance may be explored (e.g. compare subgroup of subjects who are 100% dosing compliant with subgroup of subjects <100% dosing compliant)

13.2. Adverse Events

The primary presentation of AE's will be prepared without regard to causality or relationship to study treatment. In addition, summaries of all TEAEs, treatment related TEAEs and of all SAEs will be tabulated by System Organ Class, Preferred Term, CTCAE grade, by group 1 or 2, and veledimex dose.

TEAEs

- Verbatim terms captured on the eCRF will be mapped to preferred terms (PT) and system organ classes (SOC)'s using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 23.0 or higher for purposes of treatment emergent adverse events (TEAEs) summarization. AEs will be regarded as TEAEs during the treatment period regardless of relationship to study drug if:
- The AE occurred during or after administration of the first dose of study drug (on or after Day 0: either veledimex or Ad-RTS-hlL-12),

- An already existing AE that is present when the subject is first dosed worsens in intensity during the treatment period.

Severity

The severity of AEs will be assessed for classification on a grading scale of Grade 1 to Grade 5 according to the NCI CTCAE. ATI001-102 Main initially graded adverse events per CTCAE v4.03. Administrative Memo #3 (dated 12-Nov-18) instructed the Investigators to assess all adverse events using CTCAE v5.0. Ziopharm Drug Safety and Pharmacovigilance had conducted a review of adverse events entered at that time and determined no significant impact to the grading of these adverse events. EXP Substudy used CTCAE v5.0.

Relationship (Causality)

AEs that have possibly, probably, or related relationship to the study drug are defined to be Related to the study drug. Other classifications for relatedness to study drug will be defined as Not Related. Any AEs for which the relationship to study drug is missing will be considered as related to study drug. AEs with closest relationship to the study drug will be used for summary.

Adverse Events Reporting Period

The reporting period of safety data for both studies will be from the date of ICF signature through initial Follow-up Period (day 56). AEs that are drug-related should be followed until resolved or no resolution is expected.

13.2.1. Adverse Events Number of events

Both number of events and number of subjects will be tabulated. AEs with greatest severity before baseline will be used as benchmark for comparison of AEs occurring through Day 56.

- For summaries of events, percentages will be calculated from the total number of events per group/dose cohort.

13.2.2. Summaries of Adverse Event Incidence Rates for FAS

- For summaries of subjects, the incidence percentages will be calculated from the total number of distinct subjects per group/dose cohort. If the same PT or SOC is reported more than once for a subject, the subject will only count once in the corresponding incidence of PT or SOC.
  - Where a subject has multiple adverse events in a System Organ Class I Preferred Term, only the most severe will be considered.
  - In tabulation by severity (i.e., CTCAE toxicity grade) and relationship, for a given PT or SOC, only the most severe and most closely related PT and SOC will be included for each subject.

- TEAE table summaries will be also be sorted in descending order by SOC based on the column combining over all subjects. This will also depend on the header presentation chosen. (e.g. for Table B header, this is the combined data for 52 FAS subjects or 51 ESP subjects for the group 1 veledimex treated at 20mg).

TEAEs for the following bulleted categories will be tabulated using frequency tables by dose cohort and by group, SOC and PT according to relationship to study drug, severity and seriousness for FAS OSP. All frequency tables will be presented sorted in descending order for PT for the combined tables summary within the SOC based on convention described above:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and Maximum CTCAE toxicity grade ≥ 3
- Drug-related TEAEs by SOC and PT
- Drug-related TEAEs by PT in decreasing frequency
- Serious TEAEs by SOC and PT
- TEAEs leading to death by SOC and PT, including drug related TEAE.
- TEAEs leading to treatment discontinuation by SOC and PT, including drug related TEAE.
- TEAEs leading to dose interruption by SOC and PT
- TEAEs leading to dose reduction by SOC and PT

In addition to the full listing of all AEs, separate listings for TEAEs, SAEs, AEs leading to death and AEs leading to study discontinuation will be presented.

13.2.3. Summaries of Adverse Events of Special Interest

- **Cytokine Release Syndrome (CRS)** – as defined in the Investigator's Brochure. See Section 11.1 for source information.

13.3. Laboratory Evaluations

Statistical summaries of all laboratory parameters will be converted to conventional, SI units, for the purposes of presenting descriptive statistics. Listings will present the data in the original unit collected, as well as the converted value in conventional units. A separate listing will present all units used for data collection, along with the corresponding units and conversion factors.

Absolute values and change from baseline in clinical laboratory parameters will be summarized by visit, group and veledimex dose. The incidence of normal and abnormal (subdivided into 'not

clinically significant' and 'clinically significant') laboratory values will be tabulated by visit, group and veledimex dose.

Hematology, serum chemistry, and urinalysis tests measured on a quantitative scale will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range by treatment arm as follows:

- Baseline value
- Minimum post-baseline value
- Maximum post-baseline value
- Average post-baseline value
- Last post-baseline value

Whenever available, laboratory values will be assigned toxicity grades based on the NCI CTCAE version 5.0, For some laboratory tests, these criteria may include qualifying definitions (e.g., clinical adverse event and/or requirement for concomitant medication) in addition to the specific laboratory value used for the definition of the toxicity grades. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades. Shifts in laboratory values to outside and to within the local laboratory normal range will be evaluated for selected laboratory tests by assessing, relative to the baseline value, laboratory values measured at selected time points. The number and proportion of patients with directional shifts above or below the normal range will be summarized for selected laboratory tests.

13.4. Vital signs

Vital sign parameters include height, weight, systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths/minute) and temperature (°C).

The conversion for temperature is as follows:

- Temperature (°C) = (Temperature (°F) - 32) x (*5/9)*

Absolute values and change from baseline for vital sign parameters will be summarized by visit, group and veledimex dose. Body weight (kg) will be summarized for absolute values and changes from baseline by visit and treatment arm, and overall.

All data summarized for vital signs will be provided in subject listings.

13.5. ECGs

Heart Rate (bpm), PR Interval (ms), QRS complex (ms), QT interval (ms), RR interval (ms) and QTc interval (ms) will be summarized for absolute values and changes from baseline (Screening visit) by visit, group and veledimex dose.

Overall ECG finding categories will be summarized by visit, group and veledimex dose.

Electrocardiogram results will be listed and summarized in terms of the number and percentage of patients with abnormal and normal findings, as reported by the investigator, at the time points assessed. For this study, 12-lead ECG assessments are planned at the screening visit only. Post-baseline electrocardiograms are not required unless clinically indicated.

Cardiac ejection fraction will be assessed by echocardiogram or MUGA scan at the screening visit to determine study eligibility. Patients must have an ejection fraction ≥ 40% to enroll in the study. The baseline cardiac ejection fractions will be summarized in a descriptive manner for each treatment arm. Post-baseline assessments of cardiac ejection fraction are not required unless clinically indicated.

13.6. Physical and Neurological Exam

In general, Physical examination data will be provided in patient listings listed.

Results of the targeted neurological exam will be listed and summarized by group and veledimex dose.

Clinically significant abnormalities that are identified during physical examinations will be reported as adverse events.

The disposition of each physical examination (whether performed or not) and the date the physical examination was performed will be provided in individual patient listings only. Summary tabulation of the physical examination data reported for this study is not planned.

13.7. Karnofsky Performance Status

Results of the Karnofsky Performance Status and will be summarized as a continuous variable by descriptive statistics, tabulating absolute values and changes from baseline by visit for each dose cohort treatment arm, and for all subjects combined. All subject data will be summarized in listings.

13.8. Deaths

All deaths that occur on study will be reported in a patient listing. The listing will include the primary cause of death and the number of days elapsed between Day 0 and death.

14. EFFICACY ANALYSIS

14.1. Tumor Response

Target lesion response, non-target lesion response, enhancing non-measurable lesion response, non- enhancing lesion response, new lesions, response adjusted for corticosteroid use, clinical status and objective response of the subjects according to the RANO/iRANO criteria were to be

summarized by group and veledimex dose. In addition, details of lesions including pre-baseline lesions were also to be listed.

Tumor response was to be evaluated radiographically using MRI scans to determine tumor response and to assess the time of objective disease progression (estimate of PFS). The Ad-RTS-hIL-12 injected lesion and/or other measurable brain lesions was to be measured according to the RANO/iRANO criteria guidelines.

Originally, the tumor objective response rate (ORR), progression free survival (PFS), and rate of pseudo-progression (PSP) were to be explored as surrogate endpoints for OS. In addition, the investigator assessment of tumor response was to be verified by an independent review committee (IRC) for multiple time points for each subject assessed. Because tumor response assessment produced less than the expected number of subjects with confirmed objective responses, the evaluation of ORR, has been revised and redefined for the number of times summary statistics are to be presented.

14.1.1. Objective Response Rate

The objective response rate will be summarized by group and veledimex dose on the ESP.

An exact two-sided 95% confidence interval for the percentage of responders will also be presented by visit and overall (based on the best response).

For this calculation, responders are defined as those experiencing a confirmed complete response or confirmed partial response. Non-responders are those either with stable or progressive disease. Those subjects that cannot be assessed will be treated as non-responders for the purposes of deriving the percentage of responders and confidence intervals.

The revised final tables for ORR and the 95% CI will be presented for the following.

- The ORR is reported overall by treatment arm based on the investigator response at timepoints 56 days, Week 16, Week 24, and Week 48. This is a revised subset of reporting.

14.1.2. Best Overall Response (BOR)

The best overall response (BOR) is a derived variable that summarizes for each treated subject the best tumor response recorded on the eCRF based on the investigator assessment and the IRC assessment for all:

- Tumor response data collected before evidence that the subject received a new anticancer treatment.

- Tumor response data collected regardless of whether a new anticancer treatment is recorded.

The BOR categories are defined as:

- Complete Response
- Partial Response
- Stable Disease
- Progressive Disease
- Not Evaluable (if subject has BOR assessment but is denoted Not Evaluable)
- No Response (if subject has no BOR assessment)

The BOR is evaluated for agreement statistics between the responses of the investigator assessment and the IRC for each subject.

- The IRC verification process was put on hold for the verification process planned as part of the EXP Substudy and subsequently cancelled.
- The agreement statistics between the investigator assessment and the IRC are still performed for the BOR of the subjects in ATI001-102 Main.

14.1.3. Progression Free Survival (PFS)

PFS and pseudo-progression are characterized in subject listings where applicable instead of tables.

PFS, and PSP Progression free survival was originally defined for determination of PSP requiring confirmation of progression based on RANO/iRANO criteria guidelines. Instead for reporting purposes, PFS is the time in months from the first treatment (either veledimex or Ad-RTS-hIL-12) to the first assessment on which the overall response is reported as disease progression. Subjects withdrawing from the study will be censored at their last non progressive disease response assessment. If a subject does not have a non-progressive disease response assessment, the subject will be censored on the date of the first treatment as described above.

14.2. Overall Survival

OS is defined as the duration of time from the first dose of study drug (Day 0) to the date of death from any cause in days or months. Subjects are censored based on the last date known to be alive. For example:

- Subjects who discontinue the study without documentation of additional follow-up will be censored at the date of discontinuation.
- Subjects who are lost to follow-up will be censored at last follow-up contact date.

- Subjects still alive up to 2 years from the first dose of study drug are classified as censored and as having completed all follow-up scheduling.

This could be captured on the survival page of the eCRF or the date of the subject's final assessment/ discontinuation. All summaries and analyses for primary efficacy endpoint will be based on the ESP.

14.2.1. Estimation of Overall Survival for the Monotherapy ESP

OS will be estimated and explored for three sets of subjects of the Monotherapy ESP.

- ATI001-102 Main Group 1: Craniotomy (treated at 20 mg veledimex: n=15)
- EXP Substudy: Craniotomy (treated at 20 mg veledimex: n=36)
- Combined N=15+36=51

OS data will otherwise be presented in listings for other veledimex dosing cohorts and for subjects in Group 2.

Time to OS will be estimated using the Kaplan Meier (KM) Product-Limit estimation method.

- Median survival time along with the 95% Confidence Interval (CI) will be constructed based on a log-log transformed CI for the survivor function S(t)
- OS rates at fixed timepoints (month: 6, 9, 12, 15, 18, 24) will be derived from the KM estimate.
  - The corresponding CI will be derived based on Greenwood's formula for the variance and the log-log transformation applied to the survivor function S(t)

14.2.2. Exploratory Analysis of Subject Characteristics that may Potentially Extend OS

- The Subject characteristics illustrated below have been divided into grouping variables for which the subgroup categories are well defined.
- A KM analysis for each of the grouping variables is constructed using SAS LIFETEST to compare the OS for each subgroup belonging to its respective characteristic.
- Subgroup summary statistics along with the KM plots are examined for comparability of OS for subjects treated in ATI001-102 Main with subjects treated in the EXP Substudy
  - The impact of the results observed in the combined analysis reveals whether the OS at the median is extended for one of the subgroups

- To examine the prognostic influence for subgroups treated with Ad+V on OS, a separate Cox regression for each of the grouping variables is performed using SAS PHREG,
  - Forest plot presentation is then constructed collecting the summary statistics of Cox regressions in order to display the hazard ratio estimates with corresponding 95% CI's

15. FOREST PLOT FOR 20MG COHORTS

Among the patient factors to be explored are the following patient derived variables (from the Overview Book and EDC), for ATI001-102 Main Group 1 and EXP substudy 2.0 in a forest plot.

Reference Section 11.1 for clarification on the source for the data.

Analysis using these variables (and derived variables) is an exploratory review by Ziopharm.

Age category

- <65 vs ≥65

Gender

- Female vs Male

MGMT

- unmethylated vs methylated.

Hispanic or Latino

- yes =1 vs no=0

Race

- White vs not White

IDH

- wild-type vs mutated

Prior Steroid

- yes=1 vs no=0

Enhanced Lesion

- unifocal vs Multifocal

Prior Number of Lines of Treatment

- 1 vs GT 1

cumulative dose up to 14 days

- ≤ 20mg vs >20mg

Number of Lesions at Entry

- 1 vs > 1

KPS Screening, N(%)

- ≥70 to <90 vs ≥90

Veledimex Dosing Compliance

- ≥ 80% vs <80%

Number of Recurrences

- 1st recurrence vs ≥ 2 recurrences

16. APPENDICES

Appendix 1: Schedule of Study Procedures

	Screening Period	Treatment Period								Initial Follow-up Period			Long Term Follow-up Period
Activity	**Day -28 to -1**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4-6**	**Day 7**	**Day 8-13**	**Day 14**	**Day 15**	**Day 28 ± 7**	**Day 56 ±7**	**Every 8 weeks**
Clinical Assessments													
Informed Consent	X												
Medical/Cancer History[a,b]	X												
Physical Exam[c], including targeted neurological exam	X	X	X	X	X		X		X		X		
Karnofsky PS[d]	X	X							X		X		
Height (only at Screen) and Weight	X						X		X		X		
Vital Signs[e]	X	X	X	X	X		X		X		X		
Adverse Events[f]	X →	→	→	→	→	→	→	→	→	→	→	X	
Concomitant Medications[b,f]	X →	→	→	→	→	→	→	→	→	→	→	X	X[g]
Survival Status[g]	X →	→	→	→	→	→	→	→	→	→	→	→	→
Clinical Laboratory[u]													
Pregnancy Test[h]	X	X											
Hematology Panel[i]	X	X		X	X		X		X		X		
Coagulation Panel[j]	X	X			X		X		X				
Serum Chemistry Panel[k]	X	X		X	X		X		X		X		
Urinalysis Panel[l]	X	X							X				
ECG[m]	X	X			X				X				
Registration[n]	X												
Study Drug Administration													
Ad-RTS-hIL-12		X[o,p]											
Veledimex Dose Group 1		X	X[p,q]	X	X	X	X	X	X[r]				
Veledimex Dose Group 2			X[p,q]	X	X	X	X	X	X[r]				
Veledimex Dose Compliance/Subject Diary[r]			X	X	X	X	X	X	X				

	Screening Period	Treatment Period								Initial Follow-up Period			Long Term Follow-up Period
Activity	**Day -28 to -1**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4-6**	**Day 7**	**Day 8-13**	**Day 14**	**Day 15**	**Day 28 ± 7**	**Day 56 ±7**	**Every 8 weeks**
PK/PD/Immune Assessments													
[redacted]	[redacted]				[redacted]								
Veledimex PK blood sample[s, u]		X[t]	X	X	X		X		X	X			
Serum Cytokine profile[u]		X[t]			X		X		X		X		
[redacted]		[redacted]					[redacted]		[redacted]		[redacted]		
MRI Scans[v,w]	X[v,w]			X[v,w,x]					X[v]		X[w]	X[w]	X[w]
Tumor Sample[u] (Group 1 only)		X											
CSF Sample[y] (Group 1 only)		X											

[a]: Medical history includes demographic information, medical and surgical history. Cancer history includes current cancer diagnosis, prior treatment [regimen(s), doses, start and stop dates and any associated residual toxicity], and best response for each regimen.
[b]: Medications received in the period preceding consent (~28 days) in addition to those ongoing at screening will be captured in the CRF.
[c]: A complete physical examination including a neurological exam and mental status is required at baseline. Targeted neurological exams thereafter.
[d]: See Appendix 16.1of the ATI001-102 Main Protocol (SN 0180)
[e]: Blood pressure, pulse, temperature, and respiration will be recorded. Blood pressure should be monitored closely, with hydration as needed to prevent hypotension after veledimex administration. Subjects must be instructed to maintain adequate oral hydration on and between veledimex dosing days; sites must closely monitor subjects' hydration status.
[f]: Monitoring and recording of concomitant medications and adverse events (AEs) and serious adverse events (SAEs) will be conducted throughout the study. Concomitant medications given and AEs/SAEs that occur following signed informed consent form (ICF) through the initial Follow-up Period (e.g. Day 56 visit) must be recorded in the CRF. AEs that are ongoing at the end of the Initial Follow-up Period and are considered drug related should be followed until resolution or no resolution is expected.
[g]: Patients will be followed to document start of a new anticancer therapies and survival status for 2 years following administration of Ad-RTS-hIL-12.
[h]: Females of childbearing potential will have a serum pregnancy test at the Screening Visit and a urine or serum pregnancy test on Day 0, with a negative pregnancy outcome required prior to first dose of study drug (either veledimex (Group 1) or injection of Ad-RTS-hIL-12 (Group 2)).
[i]: Hematology Panel: complete blood count, white blood count with differential, red blood cell count, hematocrit, hemoglobin, red blood cell indices, mean corpuscular volume, and platelet count.
[j]: Coagulation Panel: activated partial thromboplastin time, international normalized ratio, erythrocyte sedimentation rate and C-reactive protein.
[k]: Serum Chemistry Panel: aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, creatinine, total bilirubin, total protein, albumin, amylase, blood urea nitrogen, glucose, sodium, potassium, chloride, calcium, phosphorus and bicarbonate.
[l]: Urinalysis Panel (dipstick): appearance, pH, specific gravity, glucose, protein/albumin, blood, ketones, bilirubin, nitrates, and leukocyte esterase. In addition, a microscopic exam for casts, crystals and cells may be done if clinically indicated.
[m]: Standard 12-lead ECG; single measurement at each time point
[n]: Centralized registration of eligible subjects will be completed prior to first dose of study drug (either veledimex (Group 1) or injection of Ad-RTS-hIL-12 (Group 2)), according to a process defined by the sponsor.

[o]: Ad-RTS-hIL-12 intratumoral injection should be administered by [redacted] injection for Group 1 subjects and intracranial stereotactic injection for Group 2 subjects. Subjects must be instructed to maintain adequate oral hydration during the Treatment Period; sites must closely monitor subjects' hydration status. Because of the potential for toxicity (e.g., fevers, chills, fatigue and dehydration), administration of prophylactic antipyretics is recommended after injection of Ad-RTS-hIL-12.
[p]: Each subject will be carefully monitored for any local reactions and/or hypersensitivity reactions following the Ad-RTS-hIL-12 injection and veledimex administration. Subject should be instructed to call the clinical site if headache, hemiparesis, seizure or other local reactions develop anytime and especially between study visits.
[q]: The first postresection veledimex dose is to be given on the next day, designated as Day 1, preferably with food. Subsequent veledimex doses are to be taken once daily, in the morning and within 30 minutes of a regular meal.
[r]: Study sites must determine compliance of veledimex dosing. Subjects should be instructed to document veledimex dosing compliance in a subject diary, including the time subject took the once daily dose, the time subject ate breakfast, the number of capsules taken, whether subject missed any veledimex doses and the study day and reason for any missed doses. Study drug container(s) with any remaining capsules should be returned to the study staff, so that staff can properly assess dose compliance.
[s]: The PK sampling schedule is provided in Table 8, section 11.4 of the ATI001-102 Main Protocol (SN 0180)
[t]: Day 0, PK, and cytokine blood samples should be obtained prior to Ad-RTS-hIL-12 injection.
[u]: [redacted]. For details, see Section 11.1 through Section 11.4 of the ATI001-102 Main Protocol (SN0180) and the Laboratory Manual.
[v]: Appropriate cancer staging procedures should be performed during screening. All imaging should be of diagnostic quality. The brain is to be imaged using the same method(s) used throughout the study. Measurable target lesions should be selected and measured per RANO/iRANO guidelines. (Appendix 16.5 and 16.6 of the ATI001-102 Main Protocol (SN 0180). A repeat scan to confirm progression should be completed at 4 weeks (per RANO) and preferably again at 12 weeks (per iRANO) after first documentation of progression. Additional tumor response assessments as well as a posttreatment diagnostic brain biopsy may be performed at the discretion of the investigator as part of providing standard of care treatment in accordance with current iRANO guidelines.
[w]: The Day 28 (± 7 days) and Day 56 (± 7 days) MRI scans are required for all subjects, including those with unconfirmed disease progression, to ensure that more slowly declining tumor burden in response to therapy is noted. For 2 years, subjects without confirmed disease progression should continue to have tumor assessments performed every 8 weeks as per standard practice until disease progression has been identified (first documentation) and confirmed (12 weeks after first documentation). MRI scans should be available for collection upon sponsor request.
[x]: The MRI scan designated on Day 2 should be taken within 72 hours of Ad-RTS-hIL-12 administration and will be considered the baseline scan for tumor response assessments.
[y]: Additional tumor, CSF (if available) and blood samples to be collected, if available, as part of standard of care procedures